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INTOXICATION BY HIGH OXYGEN PRESSURES

/294**

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The intoxication by oxygen at high pressure, specifically with respect to the physiopathological problems in submarine operation and deep-sea diving, was investigated on rabbits in a caisson at oxygen pressures ranging from normal to 6 atm abs. The main purpose was to study the syndrome and development of acute and subacute oxidosis, with emphasis on the Paul Bert and Lorrain Smith effects. The poisoning, representing an association of clonic and tonic convulsions, is a reversible phenomenon which largely obeys the law of mass action. Acute oxygen intoxication is a function of various independent parameters including absolute oxygen pressure, time, living mass, velocity constants etc., expressable by an equation (which is given). Termination of exposure to high oxygen pressures after one or even several essential crises will leave no permanent damage. Hypothermia, previously considered symptomatic of acute oxidosis, exists also in the subacute form. Pulmonary lesions, considered pathognomic for subacute oxidosis, are generally encountered also in the acute form. Younger experimental animals showed greater resistance than older subjects; fasting had a protective function by increasing the resistance of the individual; an organism sensitized by a first attack was more vulnerable to repeated oxygen exposure; carbon dioxide present in small amounts in the oxygen always led to morbid accidents; barbiturates, by exerting an antagonistic action, retarded, attenuated, and even prevented convulsions but not the fatal outcome.

For several years, we have made repeated studies, for mainly practical results, on certain physiopathological problems raised by submersion in deep water.

In fact, all flexible scaphandres of the Navy and all individual rescue apparatus in service on board of submarines subject the user to the "laws of barometric pressure".

Thus, man is exposed to the possibility of various accidents which were studied in great detail by Paul Bert, including compression and specifically decompression sickness when the apparatus - case of an ordinary scaphandre - is fed with normal air.

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* Naval physicians.

** Numbers given in the margin indicate pagination in the original foreign text.

However, when an autonomous scaphandre is involved or an aqualung of the type adopted in all navies for the crews of submarines, the necessity of maintaining respiration of the divers in a closed circuit leads to replacement of normal air by pure oxygen or by a gaseous mixture rich in oxygen.

This, in turn, produces new causes for disorders, among which the hazard connected with excessive oxygen pressure in the respirable medium occupies /295 first place.

With the consent of the Members of the Academy of Medicine, we will briefly survey here the results of our research on intoxication produced by high oxygen pressures.

Ever since the famous work by Paul Bert, the study of this question, requiring a highly specialized apparatus had been abandoned entirely in France.

Intoxication by oxygen may appear under two forms, of quite distinct manifestations:

1) The first form, essentially characterized by convulsions, occurs at oxygen pressures of 4 - 5 atm abs, constituting the "mean pressure" which naturally varies with a large number of factors.

This is known as the "Paul Bert effect" which Bert had described as early as 1878 and which, at that time, was called "acute oxidosis".

2) The second form, characterized mainly by pulmonary disorders in relation with various lesions of the parenchyma (alveolitis, congestion, edema, pneumonia, etc.), develops at relatively low oxygen pressures, from about 0.7 to 1 atm abs.

This constitutes the "Lorrain Smith effect" discovered by that author in 1899, studied at numerous occasions since then, and known under the name of "subacute oxidosis"*.

1. Experimental Investigation

Our research was performed at Toulon, using an apparatus designed by us and built by the Naval Construction Bureau.

The equipment comprises a cylindrical caisson of about 1 m^3 capacity, which

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* In 1934, W.Libbrecht and L.Massart (of Ghent) suggested use of the designation "acute oxidosis" and "subacute oxidosis" for any intoxication produced by high and low oxygen pressures, respectively. We would be in favor to adopt, in honor of the discoverers, the expressions "Paul Bert effect" and "Lorrain Smith effect". It will be shown later in the text that this distinction between the two aspects of the toxigenic process is somewhat artificial since the Paul Bert effects and the Lorrain Smith effects frequently coexist, specifically at high oxygen pressures.

can be filled at will with oxygen, air, or carbon dioxide (or else with any mixture of these different gases) at pressures as high as 12 atm (gage) (13 atm abs).

Manometers, thermometers, try cocks, etc. permit controlling the pressure, temperature, and composition of the gaseous mixture.

Finally, by means of an interior illumination device and a system of adjustable mirrors which, from the outside, sweep the bull's-eyes of the caisson, it was easy to observe the behavior of the animals. /296

After a few orienting experiments with various species of animals (dog, rabbit, guinea pig), we selected the rabbit since work with this animal, when operating under exactly the same conditions and using a number of subjects of essentially the same weight, permitted a considerable reduction of the error sources inherent to individual factors.

First, we postulated the following problems:

I) Study the syndrome and evolution of acute oxidosis.
II) Determine the curve of intoxication threshold and mortality threshold under various oxygen pressures.
III) Define the principal factors liable to promote or counteract the Paul Bert effect.

In attacking these questions, we never lost sight of our ultimate goal, namely, to define the basic essentials, and apply these without delay to the organization and use of diving and submarine rescue equipment.

2. Syndrome and Evolution of Acute Oxidosis

Below, we give the routine observation of an adult rabbit submitted, in the caisson, to 6 atm abs of oxygen.

Time in Minutes	Predominating Objective Symptoms
1 to 5	Erection of the ears with dilatation and reddening of the vessels.
5 to 10	Spasms of the superciliary, orbiculary, and masticatory muscles; labial tremors; protrusion of the ocular globes.
10 to 15	Agitation, restlessness, spasmodic trembling of the extremities and of the trunk; partial or generalized rigidity; enuresis.
15 to 18	Epileptiform paroxysmal crisis with violent torsion of the trunk, carpal flexion, pedaling movement of the paws (carpopedal spasms), revulsion of the ocular globes, hyperextension of the head.

18 to 22	.....	Four new crises apparently combining general convulsions with tetanic rigidity phases.
22 to 28	.....	Alternation of three severe crises of the above type, with localized muscular twitchings (lips, masseter muscles, extremities), with muscular groups working spasmodically.
29 to 32	.....	Animal prone, immobile, bradypneic (25 - 30 respiratory movements); a few isolated clonic twitchings.
32 to 36	.....	Coma with superficial and arrhythmic respiration. Death.

Thus, the epileptiform convulsion - more or less precocious and frequent - constitutes the pathognomic syndrome of acute oxidosis. /297

At times, the convulsions are of the clonic type, consisting in partial or total spasmodic contractions.

At times, the convulsions are of the tonic type, manifesting themselves by localized or generalized tetaniform contractures.

At times, the convulsions are of a mixed type, combining rigid cramps in certain regions with myoclonic twitchings in other regions, or alternating in sequence over the entire body. Occasionally, these repeat to the point of becoming subintrant and thus constituting a veritable state of grand mal of dramatic aspect.

The so-called Paul Bert phenomenon "resembles simultaneously a strychnine crisis and an attack of tetanus".

In our opinion, it also closely resembles the convulsive syndrome of cyanogen poisoning.

Evolution. Acute oxidosis, as described above, does not necessarily lead to death. If the experiment is stopped in time, after one or even several essential crises while returning the excess oxygen pressure to normal, the general symptoms of intoxication will disappear progressively.

When placed in a normal air environment, the test subject may still exhibit a few convulsive or paretic disorders but will then recover its neuromuscular integrity, provided that the effect of the oxygen had not been of extreme intensity and of a duration to produce - directly or indirectly - definite nervous lesions.

Consequently, the Paul Bert effect is completely reversible and - under consideration of the restrictions made above - is compatible with survival of the intoxicated animal.

However, in many cases other tissue changes, not having to do directly with the general poisoning, will affect the lung and thus endanger the life of the test subject. In such a case, the Lorrain Smith effect which is not reversible

and which, erroneously, is considered as being symptomatic of subacute oxidosis, will become superposed to the first effect.

Acute intoxication by oxygen thus obeys the law of mass action. It resembles the toxigenic processes of the same order as those covered by C.Hederer and M.Istin in a general theory.

This intoxication is a function of several independent variables: absolute oxygen pressure (P), time t, living mass (M), parameters k_1 and k_2, respective velocity constants v_1 and v_2 regulating the simultaneous phenomena of intoxication and desintoxication, in accordance with the fundamental equation derived by these authors (Ref.1).

The intoxication takes place at a velocity V, given by the relation /298

$$V = v_1 - v_2 = \frac{d[PM]}{dt} = k_1[P][M] - k_2[PM].$$

This makes it entirely obvious that, in contrast to accepted concepts, it is impossible to determine separately the toxic oxygen pressure in atmospheres and in fractions of atmospheres. For example, it is impossible - as had been done by certain authors - to stipulate n kg/cm^2 for a certain species of animal and n ± 1 kg/cm^2 for another species, without committing a basic error.

Even disregarding several factors which it would be premature to discuss here, how can one dismiss the importance of the time of action?

Time, a factor which has been practically disregarded by most authors until now, actually plays a major role in all intoxications and specifically in reversible processes.

Below, we will give the proof for this statement.

3. Convulsive Intoxication Threshold and Mortality Threshold at Various Oxygen Pressures

To determine the threshold of intoxication by compressed oxygen as a function of time, with the rabbit as experimental animal, the convulsive syndrome must be taken as criterion. In this test, oxidosis is fully acute and the error sources are diminished; this is so since, between 3 and 6 atm, deviations between the various subjects of one and the same batch and submitted to the same pressure are already considerable. The mortality threshold is obtained by continuing the intoxication until death of the experimental animal. After this, the corresponding curves can be plotted point by point.

Experimental protocol. Animals of equivalent weight and subjected to the same alimentary regime are exposed, in groups of three, to a definite oxygen pressure. Their temperature is taken before and as soon as possible after the experiment.

The physical and chemical factors of the atmosphere in the caisson are practically identical for each batch: analogous temperature variations, continuous absorption of carbon dioxide by granulated soda lime, absorption of water vapor by small bags of "actigel" or "carbagel".

Each time that the intoxication is continued until death of the animal, an autopsy is performed together with an anatomicopathological examination of the lung.

The accompanying table gives an overall view, sufficient for showing the effects produced by compressed oxygen.

FATAL INTOXICATION AT 0.80 - 12 ATM ABS OXYGEN (RABBIT) /299

Oxygen Pressure, in atm abs	Average Time until First Convulsive Crisis	Average Time until Death	Average Drop in Central Temperature	Principal Pulmonary Lesions Revealed at Autopsy
0.80	-	50 to 60 hrs	0.3° to 0.5°	Alveolitis; congestion; edema of septa.
1	-	45 to 50 hrs	0.3° to 0.5°	Same lesions.
2	-	12 to 18 hrs Muscular twitchings and contractures ante mortem.	0.4° to 0.8°	Congestion; small hemorrhagic foci; slight edema.
3	3 to 5 hrs	4 to 6 hrs	0.5° to 1°	Same lesions.
4	40 min to 1½ hrs	1¾ to 3 hrs	0.5° to 1°	Intense congestion; edema; atelectasis and emphysema.
5	20 to 40 min	1 to 1½ hrs	0.5° to 1.5°	Congestion; edema and emphysema.
6	15 to 20 min	40 to 55 min	0.5° to 1.5°	Same lesions.
7	10 to 15 min	30 to 45 min	0.5° to 1.5°	Intense congestion; slight edema; peripheral emphysema.
8	8 to 11 min	25 to 35 min	0.5° to 1.5°	Same lesions.
9	6 to 9 min	20 to 30 min	0.5° to 1.5°	Same lesions.
10	5 to 7 min	20 to 25 min	0.5° to 1°	Same lesions.
11	4 to 6 min	18 to 23 min	0.5° to 1°	Congestion; atelectasis; emphysema.
12	2 to 4 min	15 to 20 min	0.5° to 1°	Congestion; edema; atelectasis and emphysema.

To reduce the occasionally large fluctuations connected with the individual factors, we entered the intoxication and mortality thresholds between the corresponding time averages.

Our results are based on protracted and numerous experiments.

4. Discussion

We will briefly review the essential elements of the toxicological problem.

1) Factors, pressure and time. Under the influence of pressure, all gases in the respirable atmosphere dissolve in the fluids and tissues of the body, in agreement with the laws of Henry and Dalton.

Thus, the accidents of acute oxidosis are in direct relation with an excess of physically dissolved oxygen since, starting from 1 atm abs, hemoglobin saturation is complete in a normal subject.

This quantity which, at 3 atm abs, is sufficient to maintain life without the participation of combined oxygen increases progressively with the pressure of the gas.

According to Behnke and coworkers, this quantity reaches, respectively, 5.45 and 7.18 cc for 100 cc of blood with 3 and 3.92 atm oxygen. These con- /300
tents, obtained by analysis, more or less correspond to the figures obtained in applying the Henry and Dalton laws.

However, Paul Bert estimated that close connections exist between the rate of flow of blood oxygen and the initiation of convulsions. He placed this rate at 30 cc per 100 cc of blood*.

In fact, our table and our curves, as stated above, indicate that the notion of "critical pressure" or of "dangerous pressure" cannot be evaluated without taking its time of action into consideration.

The two factors are inseparable over the entire extent of the curve.

Above the distinctly convulsive pressures and with an increase in pressure, the time element decreases. /301

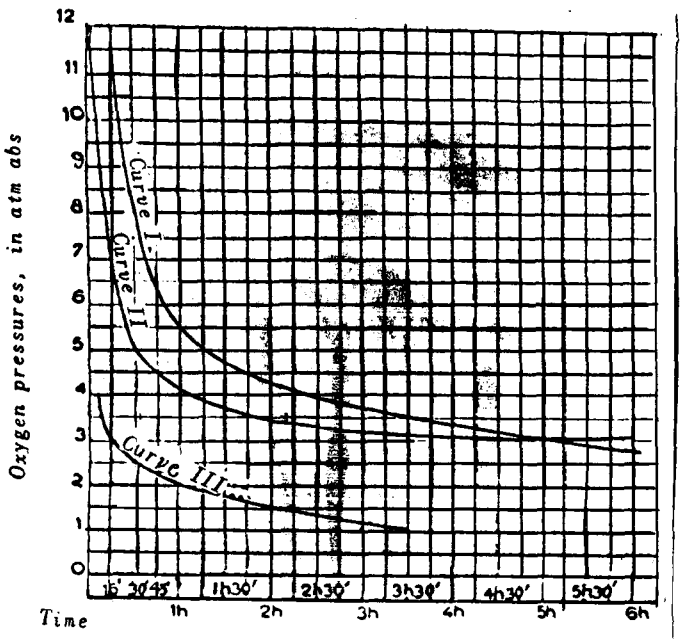
For each pressure, there exists a "mortality product" which is constant to within a few units, at least for the rabbit and under the experimental conditions used by us.

This represents an unknown application of the "Haber formula", in which the weight concentration of the toxic material must be substituted by the oxygen pressure in atm abs:

$$P \times t = M.$$

* It should be noted here that, in view of the mentioned laws and all other conditions being equal, the amount of dissolved oxygen corresponds to an equilibrium for each oxygen pressure in the respirable medium. This equilibrium may, in turn, correspond - specifically at low pressures - to a rate of oxygen flow lower than the critical percentage mentioned by Paul Bert.

This product rises from 210 to 270 between 12 and 6 atm. Beyond this, it increases still further with time, in conformity with the decrease in pressure.



Legend

Curve I: fatal intoxication threshold
Curve II: convulsive intoxication threshold
Curve III: safety threshold for man in submarine working and rescue equipment (Hederer 1933 - 1936).

This is exactly the same for all reversible intoxications (HCN, CO, CCl_3) to which Haber's formula is applied.

This necessitates a final remark: A study of the curves indicates that, in the rabbit, the limiting oxygen pressure capable of initiating the "Paul Bert effect" corresponds to 3 atm abs.

Does this mean that, below this pressure, the convulsive syndrome could not appear? It would be quite unscientific to believe so. Not only is it impossible to confine any living phenomenon within a straightjacket of figures and graphs but the toxigenic process (which we have closely followed in all its manifestations) ranges over widely differing accidents that by no means obey general rules*.

Thus, our results - under entirely definite conditions - can only reflect the average course of acute oxidosis.

2) Hypothermia. This is a constant symptom accompanying acute oxidosis and caused, according to P.Bert, by a diminution of organic combustions. We have observed this symptom in all intoxications whether ending in survival or death.

It is true that subintrant convulsions produce a temperature rise similar to that in tetanic crises. However, after this episode the thermometer drops to below normal.

Is hypothermia specific of acute oxidosis? One could easily think so when

* A study of the experimental table indicates that, below 2 atm, myoclonic phenomena and muscular contractures appear in some subjects after a time of 10 - 15 hrs. In all, this represents an incipient Paul Bert effect, which justifies our statement.

studying the literature; however, this is not the case.

Hypothermia exists already starting from very low oxygen pressures. Nevertheless, this ever-present sign of intoxication has never aroused the attention of authors who made detailed studies of all other manifestations of subacute oxidosis*. /302

Knowing that any decompression will result in a lowering of the ambient temperature, we repeated our experiments in normal air and at the same pressures, so as to eliminate any possible error. In none of the cases did the animals, decompressed at the same rate, exhibit hypothermia. Therefore, one can state that the decrease in central temperature constitutes a physiological sign of effects produced in the organism by a toxic oxygen pressure.

However, our figures have only an indicative value since the time necessary for the decompression and the handling of the caisson made it impossible to immediately measure the temperature of the intoxicated animals.

3) Anatomicopathological lesions. Anatomicopathological studies of acute oxidosis still remain to be made, or at least a histopathological study of the nervous system, since this would throw some light on the still so obscure pathogeny of intoxication.

At present, only pulmonary lesions characterizing the Lorrain Smith effect are known thoroughly. These appear more or less rapidly, depending on the susceptibility of the animal species treated, above 0.60 and 0.70 atm abs of oxygen.

In rabbits kept for 48 hrs under a pressure of one atmosphere, examination of the lungs showed the following picture**:

a) intense and rutilant congestion***;
b) edema due to thickening of the interaveolar septa or total edema with occasionally hemorrhagic transudation;
c) degeneration of the epithelium with desquamation, cellular hypertrophy and hyperplasia, presence of fibrin (typical picture of

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* P.Bert (1878), L.Hill, and J.J.R.MacLeod (1903) mentioned a temperature drop only in convulsive intoxications. Behnke, Johnson, Poppen, and Motley (1935), who exposed human subjects in caissons up to 4 atm oxygen and studied the modifications of various physiological constants, completely neglected the thermal curve. In the interesting study by Binet, Bochet, and Bour (1938), devoted to subacute oxidosis up to 1 atm of pure gas, there is also no mention of temperature variations.

** All histopathological examinations were made at the laboratory of the Sainte-Anne Hospital by our colleagues and friends, the chiefs of staff Le-Chuiton and Bideau.

*** Hyperoxygenation of the blood actually produces a brilliant bright red coloration in all organs. This phenomenon is more accentuated than in intoxications by carbon monoxide or by hydrocyanic acid.

pneumonia).

In addition, emphysema and atelectasis are encountered. Emphysema may be caused by a compensating superventilation of the undamaged areas of the lung and specifically by the expansion of gases during decompression (residual nitrogen).

Atelectasis which frequently is produced during a rapid compression also characterizes the inflammatory irritation of the parenchyma. /303

All these lesions or analogous changes have been mentioned, ever since Lorrain Smith, by various other authors: L.Hill and MacLeod (1903), A.Adams (1912), Achard, Binet, and Leblanc (1918), Ch.Richet (1927), and others.

From our own work, we obtain the following results:

1) The Lorrain Smith effect is not characteristic for intoxication at low pressure.

2) It is impossible, as had been done by certain authors, to consider the convulsive action and the pulmonary action of oxygen as an expression of high or low pressures, respectively. We were able to demonstrate their coexistence from the top to the bottom of the curve. It should be mentioned also that the "pressure factor" actually intervenes to a considerable extent in accelerating the development of respiratory lesions. Within 15 - 20 min at a pressure of 6 - 8 kg/cm^2, we observed already an intense vascular congestion, forming the starting point for edematous reactions that constitute a proof for the irritating properties of oxygen!

4. Individual Factors Promoting or Inhibiting the Development of Acute Oxidosis

Under this category, we will group all individual factors and some extraneous factors that are able to influence the Paul Bert effect.

1) Animal species. P.Bert mentioned already that birds (sparrows, linnets) are much more sensitive than mammals. In these, already 2.8 atm oxygen will produce convulsions; in the dog, at least 4 atm are necessary for inducing convulsions.

Rabbits are also more sensitive than dogs and react more rapidly to the same pressure. However, these fine gradations which, in themselves, are unimportant change nothing in the crux of the matter.

2) Age. Young animals have a greater resistance than old ones to high oxygen pressures (Massart, 1934; Prikoadowizky, 1936).

Our own tests confirmed the results obtained by these authors. Convulsions are always retarded, less frequent, and less accentuated in young rabbits than in adult subjects.

3) State of fasting. The role of fasting has been demonstrated by Ozorio de Almeida (1934). We agree with this author in postulating that the fasting state increases the tolerance of animals for oxygen. At a pressure of 4 atm, rabbits that had been kept on a strict fast for 72 hrs showed no convulsions after 4 hrs of staying in the caisson. Some rigidity and tremors were observed on return to normal air*. Death intervened between 8 and 13 hrs by pulmo- /304
nary lesions. A study of the accompanying table shows that, without previous fasting, the animals always exhibited crises before the second hour and succumbed near the third hour.

4) Sensitization. Just like many medicinal or toxic agents, oxygen sensitizes the organism.

Thus, rabbits subjected to a pressure of 2 atm for a period of 8 hrs and then removed from the caisson without apparent trouble except for a slight hypothermia (-0.3, -0.7°) were subjected, 20 hrs later, to the same pressure. They died, after 5 - 7 hrs of stay in the caisson, under gross pulmonary lesions after having presented, in the pre-mortem period, rigidity and spasmodic tremors, signs of an incipient general intoxication.

All control animals, exposed for the first time with the above animals, survived.

Consequently, oxygen is able to sensitize the organism and the pulmonary tissue to a subsequent attack. It also determines a state of hyperreflexia and hyperexcitability which persists for several hours after leaving the caisson.

This notion is of some interest for the application of oxygen in submarine work and in therapeutics.

5. Chemical Actions Promoting or Inhibiting Development of Acute Oxidoxis

The list of agents susceptible of modifying the toxigenic process, in one direction or another, probably is extremely long. We were able to only skim over this aspect of the problem, so as to deduce a few practical indications.

1) Action of carbon dioxide. In submarine diving equipment, supplied with oxygen in a closed circuit, the level of carbon dioxide may reach an excessive height if, for any reason whatever, the purification of the expired gases is insufficient.

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* We found, during reversible intoxications at different pressures, that the animals frequently went into convulsions on removal from the caisson. Occasionally, the convulsive process continued for quite some time after the experiment in the form of brief general crises, clonic twitchings, and localized contractures. Paretic or paralytic phenomena were not uncommon. These indicate the probable existence of nervous lesions (specifically of the medullar type). Here again, histological changes due to decompression must not be attributed to oxidosis as the cause!

Since the toxicity of carbon dioxide increases proportionally to the product of its percent content in the atmosphere by the pressure of this atmosphere, it is obvious that a percentage of 1 - 1.5, innocuous at 760 mm Hg, /305 will become physiologically highly active at 40 m depth (5 atm abs).

These 5 - 7.5% of carbon dioxide actually promote the development of oxidosis, as shown in research by L.Hill, by Massart, and in our own experiments which confirmed their results.

In the rabbit, 5 - 7% carbon dioxide in the oxygen, compressed to 3 atm, initiate the appearance of premonitory disorders (tremors, twitchings, muscular fibrillation) and the appearance of the full convulsive syndrome.

Massart estimated that the hyperventilation produced by carbon dioxide might explain this phenomenon since it accelerates the diffusion of oxygen in the metabolism*.

2) Action of strychnine. The symptomatology of acute oxidosis clearly resembles the effects of strychnine. It seemed of interest to determine whether strychnine, by increasing the nervous excitability of the subject, might promote the toxigenic process and aggravate it. Below, we furnish the answer to this question.

A. Two groups of rabbits, selected and prepared in accordance with an invariant protocol, were enclosed in the caisson under 2 atm abs of oxygen; the first group previously received 0.8 mg of strychnine per kg, while the second group was given nothing.

a) At the end of 9 hrs, the strichninized animals died under violent convulsions.

b) At the end of 12½ hrs, the control rabbits exhibited no convulsions. They were removed from the caisson, apparently undamaged; nevertheless, they died the next day with gross pulmonary lesions.

B. On repeating this experiment at a pressure of 7 atm, the action of strychnine was even more pronounced.

a) The strichninized rabbits, which went into convulsions after the 3rd and 4th minute, died between 19 and 23 min.

b) The control rabbits suffered their first crisis close to the 12th or 13th minute and died between 30 and 40 min.

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* L.Binet and coworkers (1938) reported the following experiment: A batch of eight mice was kept for 4 days in pure oxygen at normal pressure. Due to the fact that the experimenter forgot to change the soda lime, the carbon dioxide increased during the night and reached a content of 6%. At the moment of opening the bell jar, four mice died under convulsions. This result was of interest not only since it emphasizes the effect of an O_2 + CO_2 mixture but also since it demonstrates the fragility of the barrier separating the Paul Bert from the Lorrain Smith effect.

In summary, it can be stated that high oxygen pressures and strychnine combine their effects. Thus, oxygen seems to act as a medullary poison, which constitutes a rather simple hypothesis since its "pharmacodynamics" is still relatively unknown!

3) Action of barbiturates. P.Bert demonstrated that chloroform anesthesia prevented the appearance of convulsions (or had a subduing effect) without, /306 however, stopping the fatal process of the poisoning.

In the hope of finding a suitable palliative for acute oxidosis, we used the antagonistic action of barbiturates, specifically of gardenal (phenobarbital). We started from the fact that the Paul Bert syndrome reflects quite faithfully the typical picture of strychnine poisoning, on which barbiturates have an elective action.

The experimental series confirmed our hypothesis.

A. Two groups of rabbits, one used as controls and the other "gardenalized" with 0.02 gm of soluble product per kilogram body weight were subjected to 9 atm abs of oxygen for a period of 25 min.

a) The normal rabbits, which entered convulsions after the 7th and 8th minute, died after about 20 min.

b) The gardenalized rabbits presented an attenuated convulsive syndrome between 20 and 25 min. When removed from the test zone, they died of acute pulmonary edema between $3\frac{1}{2}$ and 5 hrs.

B. The second experiment was made with exposure to 7 atm for 35 min, doubling the gardenal dose.

a) The normal rabbits, which went into convulsions toward the 12th and 14th minute, died between the 29th and 34th min.

b) The gardenalized rabbits showed no convulsions. They remained completely immobile. When removed from the caisson they died after 20 hrs, with respiratory lesions and without having come out of the barbituric coma.

Thus, gardenal will retard, attenuate, and - in massive doses - prevent convulsions. It is also able to noticeably differentiate the death. The antidote effect of barbiturates thus is of some interest for prophylaxis of acute oxidosis in working and rescue operations of crews in submarines in deep water as well as for rapid treatment of "caisson disease" by oxygen under pressure.

6. Conclusions

1) The intoxication by oxygen may cover two aspects that are quite distinct in appearance:

The first aspect, characterized by epileptiform convulsions, is produced

above about 4 - 5 atm and represents the "Paul Bert effect" or "acute oxidosis".

The second aspect, characterized by lesional irritation of the lung, develops at low pressure starting at 0.70 to 0.80 atm and is known as the "Lorrain Smith effect" or "subacute oxidosis".

2) In this paper, the authors (who, for practical reasons, have resumed experimental studies on acute oxidosis which had been neglected in France ever /307 since Paul Bert's time) demonstrate the following:

a) This poisoning, constituting an association of clonic and tonic convulsions, represents a reversible phenomenon which "on the whole" obeys - as all processes of the same order - the law of mass action.

b) For appreciating the toxicity of oxygen it is necessary not only to consider the gas pressure but also the combination of this pressure and its time of action.

3) Working with rabbits, two curves are thus established: one corresponding to the convulsive intoxication threshold and the other to the fatal intoxication threshold between 0.80 and 12 atm abs oxygen.

4) In studying the temperature variations and the pulmonary tissue changes in the intoxicated animals, the following was demonstrated:

a) Hypothermia, believed to be symptomatic for acute oxidosis, exists also in the subacute form.

b) The pulmonary lesions, regarded as pathognomic for subacute oxidosis, are also generally present in the acute form.

c) These two more or less pronounced effects (jointly or independently) emphasize over the entire slope of the curve the double toxicity, general and local, of oxygen.

5) In studying the principal individual factors promoting or inhibiting the Paul Bert effect, the following was found:

a) With respect to age, the tolerance of young animals is greater than that of old subjects.

b) The fasting state plays a protective role, by increasing the resistance of the individual.

c) The organism, sensitized by a first attack, shows a greater vulnerability to the repeated action of oxygen.

6) In studying the chemical reactions capable of influencing the course of the toxigenic process, the following was mentioned:

a) Carbon dioxide, when present at a low percentage (5 - 7%) in the oxygen, will always precipitate - at a given pressure - the onset of morbid accidents.

b) Strychnine, superposing its effects to that of oxygen, accelerates and aggravates - even at very small doses - the development of intoxication.

c) Barbiturates, exercising an antagonistic effect, will retard, attenuate, and even prevent the convulsions.

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